REMARKS

Reconsideration of the allowability of the present application is requested respectfully.

Status of the Claims

Claims 1 to 6 were acted upon by the Examiner in the Office Action dated March 25, 2003. Claims 7 to 11 were withdrawn. Claims 1, 3, and 5 have been amended. Claims 2, 4, and 6 have been cancelled. Claims 12 to 30 have been added. Accordingly, Claims 1, 3, 5, and 12 to 30 are presented for examination.

Support for newly presented Claim 12 and 13 can be found throughout the application, particularly on page 13, line 1 to page 14, line 17. Support for newly presented Claim 16 can be found throughout the application, particularly on page 10, lines 3 to 6. Support for newly presented Claims 17 and 18 can be found throughout the application, particularly on page 5, lines 11 to 19. Support for newly presented Claims 14, 15, and 19 to 22 can be found throughout the application, particularly on page 27, line 12, to page 29, line 2, and page 42, line 8, to page 44, line 11. Support for newly presented Claims 23 to 30 can be found throughout the application, particularly on pages 17,line 17, to page 18, line 3.

Affirmation of Sequence Election

Applicants affirm the election of SEQ ID NO:2.

ARGUMENTS

In response to the Examiner's Office Action dated March 25, 2003, Applicants respectfully traverse the Examiner's rejection of Claims 1, 3, and 5.

Summary of the Invention

Applicants have identified membrane translocating peptide sequences, along with fragments, motifs, derivatives, analogs and peptidomimetics thereof (hereafter "MTLPs") that enhance the cellular uptake of pharmaceutically active agents. Multiple MTLP sequences are disclosed. The MTLPs may comprise L- or D-form amino acids or molecular analogs of amino acids, and may also be linear or cyclic molecules. The MTLPs may be generated by expression of a polynucleotide encoding the MTLP or by chemical synthesis. Prior to applicants' invention, the presently claimed MTLP sequences had not been disclosed. Furthermore, particles comprising MTLPs that enhance uptake of an agent had not been previously described. Thus, applicants have advanced the state of the art by providing for the first time the means which enable those in the field to increase the uptake of pharmaceutically active agents.

Applicants have further advanced the state of the art by providing means for generating MTLP/particle complexes that enhance the uptake of pharmaceutically active agents. Such MTLP/particle complexes include, but are not limited to, particles such as a microparticle, a nanoparticle, or a liposome. Use of such an MTLP/particle complex to transfer polynucleotides into a cell results in a higher expression of the gene encoded by the polynucleotide as compared to particles lacking MTLPs.

While not wishing to be bound by a theory respecting the reason for the effectiveness of applicants' development, applicants believe that the MTLP helps improve the interaction of an agent or particle with a cell membrane thus increasing the efficiency of transfer of the agent across the cell membrane.

Before discussing the Examiner's art rejections in detail, applicants believe it will be helpful to review the publications relied on by the Examiner.

Summary of the Cited Art

U.S. Patent No. 6,248,558, Lin et al., discloses the generation of fusion proteins comprising the peptide sequence AAVLLPVLLAAP (hereafter "MTS sequence"). Presence of the MTS sequence in the protein facilitates the importation of the protein into NIH3T3 fibroblasts. There is no disclosure of utilization of transfection using an MTS that is not covalently linked to another molecule. Furthermore, the publication does not disclose the use of liposomes to facilitate transfection.

U.S. Patent No. 4,847,240, Ryser et al., discloses the use of poly-lysine polypeptides that are covalently linked to molecules in order to facilitate the uptake of the molecules into cells.

The §112 Rejections

The Examiner has rejected Claims 1 to 6 under 35 U.S.C. §112, first paragraph, because the specification does not provide reasonable enablement for all derivatives, fragments, motifs, analogs and peptidomimetics of all the peptides of SEQ ID NOS: 2, 3, and 14 to 22.

Claim 1, and dependent Claims 3 and 5, require "A composition, comprising a peptide having an amino acid sequence substantially as set forth in SEQ ID NO: 2 and a derivative, fragment, motif, analog or peptidomimetic thereof (MTLP).". Applicants have amended Claim 1 to remove reference to "a derivative, fragment, motif, analog or peptidomimetic thereof (MTLP)" of the peptides of SEQ ID NOS: 2 or 3. Claims

2, 4, and 6 have been cancelled. Thus, this amendment should obviate the Examiner's rejections under 35 U.S.C. §112, first paragraph.

Applicants respectfully request the withdraw of the rejections to Claims 1, 3, and 5 under 35 U.S.C. §112, first paragraph.

The §102 Rejections

The Examiner has rejected Claim 1 to 6 under 35 U.S.C. §102(e) as being anticipated by Lin et al. Lin et al. discloses sequences identical to SEQ ID NO: 15, and 17 to 22 of the present application. The Examiner asserts that such sequences can also be considered a derivative, fragment, motif, analog or peptidomimetic of SEQ ID NOS: 2, 3, and 14 to 22. Applicants have amended Claim1 to remove reference to "a derivative, fragment, motif, analog or peptidomimetic thereof (MTLP)" of all the peptides of SEQ ID NOS: 2, 3, and 16. Claims 2, 4, and 6 have been cancelled. Thus, the matter of Claim 1 is no longer covered by Lin et al. and this amendment should obviate the Examiner's rejections under 35 U.S.C. §102(e).

Applicants respectfully request the withdraw of the rejections to Claims 1, 3, and 5 under 35 U.S.C. §102(e) in view of Lin et al.

The Examiner has rejected Claim 1 to 6 under 35 U.S.C. §102(e) as being anticipated by Ryser et al. Ryser et al. discloses the use of poly-lysine polypeptides that are covalently linked to molecules. The Examiner asserts that such sequences can also be considered a derivative, fragment, motif, analog or peptidomimetic of, for example SEQ ID NOS: 2 and 3. Applicants have amended Claim 1 to remove reference to "a derivative, fragment, motif, analog or peptidomimetic thereof (MTLP)"

of all the peptides of SEQ ID NOS: 2, 3, and 16. Claims 2, 4, and 6 have been cancelled. Thus, the matter of Claim 1 is no longer covered by Ryser et al. and this amendment should obviate the Examiner's rejections under 35 U.S.C. §102(e).

Applicants respectfully request the withdraw of the rejections to Claims 1, 3, and 5 under 35 U.S.C. §102(e) in view of Ryser et al.

The §103 Rejection

The Examiner has rejected Claims 1 to 6 under 35 U.S.C. §103(a) as being unpatentable over Lin et al. in view of Ryser et al. Lin et al. discloses the amino acid sequence AAVLLPVLLAAP. Ryser et al. discloses the use of poly-lysine polypeptides (KK or KKK) that are covalently linked to molecules. The Examiner asserts that it would have been obvious to one of skill in the art to combine Lin et al. with Ryser et al. in order to make the claimed invention.

Applicants respectfully traverse the rejection.

MPEP §2143 requires that "the prior art reference (or references when combined) must teach or suggest all the claim limitations." The Examiner asserts that adding the amino acids KK or KKK to the sequence disclosed in Lin et al. would result in the peptides KKAAVLLPVLLAAP and KKKAAVLLPVLLAAP. The Examiner further asserts that these two new peptides are identical to SEQ ID NOS: 2 and 3 of the present invention, respectively. This is incorrect. The amino acid sequences of SEQ ID NOS: 2 and 3 are KKAAAVLLPVLLAAP and KKKAAAVLLPVLLAAP, respectively. SEQ ID NOS: 2 and 3 have an extra alanine residue. Thus, the

combination of Lin et al. and Ryser et al. does not teach or suggest all the claim limitations.

Page 16, lines 10 to 17, of the application recite:

> The 15 residue hydrophobic peptide ZElan094 (SEQ ID NO:2) is related in sequence tot he 12 residue hydrophobic peptide sequence AAVLLPVLLAAP (SEQ ID NO:1) (Rojas et al. Nature Biotechnology 16:370, 1998). However, the 15 residue ZElan094 differs from the 12 residue SEQ ID NO:1 in that it has three additional amino acid residues, KKA, at the N-terminus and a blocking amide at the C-terminus. These N-terminus and C-terminus modifications are designed to enhance the solubility and the *in vivo* stability of the MTLP, respectively. The NH2 terminus alanine also may contribute to the alpha helical properties of the peptide.

It is clear from the above passage that the addition of this alanine residue was intentional. Furthermore, the addition of the KKA or KKKA motif does not relate solely to the membrane translocatability of the peptides, since these motifs can affect solubility and the secondary structure of the peptides. In particular, the alanine residue may contribute to the alpha helical properties of the peptides.

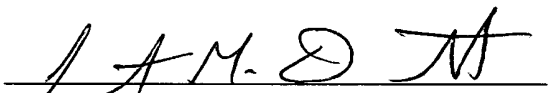
Furthermore, MPEP §2141 requires that objective evidence such as unexpected results be considered when evaluating whether an invention is obvious. In the present application, Table 6 on page 43 of the application provides such evidence. Table 6 depicts results wherein the inclusion of peptides comprising SEQ ID NO:2 in a liposome mixture resulted in either a 387% or 260% increase in transfection efficiency. There are no disclosures in the prior art, including Lin et al. and Ryser et al., that are predictive of this dramatic and unexpected increase in transfection efficiency.

Claims 2, 4, and 6 have been cancelled. Therefore, applicants respectfully request the withdraw of the rejections to Claims 1, 3, and 5 under 35 U.S.C. §103(a) as being unpatentable over Lin et al. in view of Ryser et al.

A Petition for extending the period to respond to the Examiner's Action for two months, from June 25, 2003 to August 25, 2003, is enclosed.

Respectfully submitted,

SYNNESTVEDT & LECHNER LLP



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Enclosures

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